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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MYERS, CARLA J

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,113	TYRRELL ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,26,27,32-36 and 39-62* is/are pending in the application.

4a) Of the above claim(s) *35,42-53 and 55-62* is/are withdrawn from consideration.

5)☒ Claim(s) *13,39 and 40* is/are allowed.

6)☒ Claim(s) *26, 27, 32-34, 36, 41, 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the amendment filed April 2, 2003. Applicants arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

2. This action contains claims 42-62 and the subject matter of SEQ ID NO:3-7, 9-14, and 16-23, non-elected with traverse in the response of Paper No. 14. In the response filed April 2, 2003, Applicants state that upon allowance of claims 32-34, the restriction requirement should be withdrawn. However, as detailed below, claims 32-34 are not allowable. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee (GenBank Accession No. AF042820).

Claim 26 is inclusive of oligonucleotides comprising SEQ ID NO: 15. Because of the open claim language "comprising", the claims include oligonucleotides which contain SEQ ID NO: 15 and any number of flanking nucleotides. Lee (GenBank Accession No. AF042820) teaches nucleic acids comprising the 24S large subunit ribosomal RNA sequence of *Heterosigma akashiwo*. The complementary inverse strand of this rRNA contains the 22 mer nucleotide

sequence of SEQ ID NO: 15 (see nucleotides 127-149 of the rRNA of Lee). Accordingly, the oligonucleotide of Lee anticipates the invention of claims 13, 16 and 26. With respect to claims 27, the inverse complementary strand of the rRNA of Lee also contains the nucleotide sequence of the 22 mer of SEQ ID NO: 8 (see nucleotides 58-78 of the rRNA of Lee). The rRNA of Lee contains multiple copies of the rRNA nucleic acids and thereby Lee is considered to teach compositions comprising the pair of oligonucleotides containing SEQ ID NO: 15 and SEQ ID NO: 8.

RESPONSE TO ARGUMENTS:

In the response of April 2, 2003, Applicants traverse this rejection with respect to claim 26 by stating that Lee does not teach a probe having the repeat structure of $[X\text{-}Y\text{-}Z]_n$. However, it is noted that "n" may be 1 and thereby the structure of [X-Y-Z] need not be repeated. Applicants state that Lee does not teach a component X that is a sequence of "1 to 100 nucleotide analogs" or a sequence Z that "is a sequence of 1 to 100 nucleotides and nucleotide analogs". However, as written the claims include an X sequence that may be **0** to 100 nucleotides and a Z sequence that may be **0** to 100 nucleotides. Thereby, claim 26 is inclusive of probes **comprising** (i.e., containing any number of flanking nucleotides) $[Y]_1$. Accordingly, the claims read on the sequence of Lee which comprises SEQ ID NO: 15 ("Y"). Even if the claims were amended so that X and Z were defined as being a sequence of 1 to 100 nucleotides, the sequence of these nucleotides is not defined in the claims in terms of their identity. Thereby, the claims would still read on the sequence of Lee which comprises SEQ ID NO: 15.

With respect to claim 27, Applicants state that Lee does not teach a pair of oligonucleotides, but rather teaches only a single oligonucleotide that is complementary to either SEQ ID NO: 15 or 8. This argument is not persuasive because the claims do not require that the oligonucleotides are distinct from one another. A pair of oligonucleotides includes 2 oligonucleotides that may be of the same identity. Further, the claims recite the open claim language "comprising" and thereby include any number of nucleotides flanking the sequences of SEQ ID NO: 15 and 8. Thereby, the claims read on the oligonucleotides of Lee which each comprise SEQ ID NO: 15 and 8.

4. Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Asai (Nippon Kagakkai Koen Yokoshu, 1998, Vol. 75, page 315).

Asai teaches a method for detecting the raphidophyte *Heterosigma akashiwo*. In the method of Asai, the nucleic acids of *H. akashiwo* are released from the cell (which is considered to be a step of permeabilizing a cell to expose ribosomal RNA), the 18S rRNA sequences are hybridized with oligonucleotide primers and amplified by PCR (which is considered to be a step of contacting RNA with a probe capable of hybridizing to a hypervariable region) and the amplified PCR products are detected as indicative of the presence of a raphidophyte cell (which is considered to be a step of identifying hybridization complexes). Asai teaches that this method is useful for monitoring samples for the presence of the red tide phytoplankton *H. akashiwo* since this organism is associated with causing fish death.

RESPONSE TO ARGUMENTS:

In the response filed April 2, 2003, Applicants traverse this rejection by stating that Asai does not "disclose, mention or hint at RNA having "hypervariable regions". However, as broadly written the claims include probes "capable of selectively hybridizing" to hypervariable regions. The claims do not recite the conditions under which this hybridization may occur and thus the claims include probes that could hybridize under some unstated conditions to hypervariable regions. Further, the term "selectively" is not clearly defined in the specification. This term has been interpreted to mean that the probe may bind to some higher degree to a hypervariable region than to another unstated sequence. Applicants are arguing limitations not recited in the claims. The claims are not limited to probes which bind only to hypervariable regions-i.e., probes consisting of a sequence that binds only to a hypervariable region. The 24S RNA of Lee has each of the functions and properties for the probes required by the claims. That is, the 24S rRNA contains hypervariable sequences which would hybridize to a higher degree to hypervariable regions to form a hybridization complex. There is no requirement in the claims for the reference to specifically teach that the probe binds to a hypervariable region.

Applicants further state that Asai does not teach identifying a hybridization complex made by the primer and the 18S rRNA. However, Asai does teach detecting the amplification PCR products. The amplified PCR products contain the primer and the amplified target sequence and thereby are considered to be a "hybridization complex". By detecting the amplified PCR products, the method of Asai necessarily identifies the hybridization complex.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-34, 36, 41 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asai in view of Scholin (reference "22" cited in the IDS filed February 9, 2001) and Lee.

Asai teaches a method for detecting the raphidophyte *Heterosigma akashiwo*. In the method of Asai, the nucleic acids of *H. akashiwo* are released from the cell, the 18S rRNA sequences are hybridized with oligonucleotide primers and amplified by PCR and the amplified PCR products are detected as indicative of the presence of a raphidophyte cell. Asai teaches that this method is useful for monitoring samples for the presence of the red tide phytoplankton *H. akashiwo* since this organism is associated with causing fish death. Asai does not teach detecting

H. akashiwo using a method of in situ fluorescent hybridization or a method of sandwich hybridization.

Scholin teaches methods for detecting microalgal species in environmental samples. Scholin teaches that microorganisms can be detected using either a fluorescent *in situ* hybridization methods or a sandwich hybridization method (see pages 192-193). The reference also teaches that these methods provide several advantages. In particular, the sandwich hybridization method a very rapid, easy and automatable means for detecting a microorganism and the fluorescent *in situ* hybridization method provides a means for analyzing the labeled cells individually and for purifying labeled cells by cell-sorting flow cytometry (see page 195). The reference further teaches methods for identifying LSU rRNA probes useful for performing the detection methods and teaches that the LSU rRNA is useful as a probe because it contains hypervariable sequences and because rRNA is present in the cell at a high copy number, thereby increasing the sensitivity of the detection method. Scholin also teaches the reagents necessary to perform the disclosed hybridization method, including the reagent of hybridization buffer (see page 192-193). Additionally, the 24S rRNA sequence of *H. akashiwo* was known at the time the invention was made and is specifically taught by Lee.

In view of the teachings of Scholin and Lee, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Asai so as to have detected *H. akashiwo* using the sandwich hybridization or fluorescent in situ hybridization assay of Scholin in order to have provided an equally effective means for detecting

H. akashiwo and to have provided sandwich hybridization methods which could be performed rapidly and in an automated format and to have provided fluorescent *in situ* hybridization methods which could be used to identify and isolate the positively labeled *H. akashiwo* cells. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the 24S rRNA sequences of Lee comprising the 22 mer of SEQ ID NO: 15 as a probe since Scholin teaches that the LSU rRNA provides a useful probe for detecting microorganisms. While it is noted that the specification (page 36) teaches the improved results obtained when using probes consisting of SEQ ID NO: 15, the claims are broadly drawn to probes and methods of using probes comprising SEQ ID NO: 15. Accordingly, these improved results do not apply to the claims as they are broadly written and, as discussed above, the prior art when considered as a whole would have lead one of skill in the art to detection methods using probes comprising SEQ ID NO: 15.

RESPONSE TO ARGUMENTS:

In the response filed April 2, 2003, Applicants traverse this rejection by stating that none of the cited references teach that raphidophytes rRNA contains hypervariable regions or the locations of the hypervariable regions. This argument is not convincing because the combined references teach using the full length 24S rRNA as a probe. It is a property of this 24S rRNA that it contains hypervariable regions. As discussed above, Scholin teaches that the 24S rRNA is useful as a probe because it contains hypervariable sequences. Further, those of ordinary skill clearly understand that it is a property of all LSU rRNA (i.e., 24S rRNA) that they contain

hypervariable regions. Secondly, there is no requirement for the cited references to teach the location of hypervariable sequences since the claims are not limited to probes which consist of only sequences that bind to a hypervariable region. The claims as broadly written include probes "capable of selectively hybridizing" to hypervariable regions and thereby include probes that could hybridize under some unstated conditions to hypervariable regions and which hybridize to some degree more to a hypervariable region than to some other unstated region. The probes required by the claimed methods are inclusive of the 24S rRNA of Lee since this rRNA contains hypervariable sequences which would hybridize to a higher degree to hypervariable regions to form a hybridization complex. Applicants state that Asai does not teach detection of a hybridization complex. However, the rejection is based on the combination of references of Asai, Scholin and Lee. As discussed above, Scholin teaches in situ hybridization methods which detect the formation of a hybridization complex between a target sequence and a probe. Applicants state that the references do not teach selecting a probe comprising SEQ ID NO: 15. However, Scholin teaches using the LSU rRNA as a probe and Lee teaches the 24S rRNA of *H. akashiwo,* which comprises SEQ ID NO: 15. Accordingly, the combined references do in fact suggest in situ hybridization methods using a probe comprising SEQ ID NO: 15. Applicants argue that the combined references do not teach designing probes to a variable region of raphidophyte rRNA. However, the claims are not limited to methods which require such probes. Applicants argue that there is no reasonable expectation of success because the references do not provide sufficient instructions for identifying hypervariable sequences. However, again, the claims are not limited to

methods which utilize probes consisting only of sequences complementary to a hypervariable region. In view of the disclosure of Asai, Scholin and Lee, the ordinary artisan would have had more than a reasonable expectation of success of using the 24S rRNA of Lee in the in situ hybridization method of Scholin in order to detect a raphidophyte cell as disclosed by Asai. Applicants argue that it takes extensive experimentation to identify probes that are capable of selectively hybridizing to hypervariable regions and which could be used to identify a raphidophyte cell. However, claims 32-34 are not in fact limited to any particular sequences of a hypervariable region and therefore it is unclear as to how Applicants can argue that extensive experimentation is required to identify specific hypervariable rRNA sequences when the claims are not in fact limited to probes consisting of any specific hypervariable sequences.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

June 17, 2003

CARLA J. MYERS
PRIMARY EXAMINER